REMARKS

I. Status of the claims

Claims 86, 94-98, 100-102, 110-111, and 114-119 are pending and under examination. Claim 112 has been cancelled without prejudice. No new amendments have been added in this response.

II. Rejection of claims 86, 100-102 and 110-119 under 35 U.S.C. § 103

Claims 86, 100-102 and 110-119 were rejected under 35 U.S.C. § 103 as being unpatentable over the combination of Kay, Fosnaugh, Frechet, and Florence. Applicants respectfully traverse this rejection.

Claim 86 recites a double-stranded ribonucleic acid (dsRNA) comprising a complementary RNA strand, a sense RNA strand and only one lipophilic group having a $\log K_{ow}$ exceeding 1. The complementary RNA strand has a nucleotide sequence which is complementary to a target RNA, and wherein the target RNA is an mRNA transcript of a target gene or of a (+) strand RNA virus. The lipophilic group is covalently attached to a 5'-end of the complementary RNA strand and a linkage between the lipophilic group and the 5'-end of the complementary RNA strand comprises a phosphodiester group.

Kay is cited for the teaching of dsRNA that efficiently inhibit viral gene expression, and targeting hepatocyte cells using a dsRNA molecule capable of inhibiting the expression of a Hepatitic C Virus. See Office Action mailed March 19, 2009, page 4. Kay does not teach, nor is Kay cited for the teaching of a lipophilic group linked at the 5' end with a phosphodiester group as required by the pending claims. The examiner cites Fosnaugh for teaching a dsRNA that comprises a conjugate covalently attached to the dsRNA, with broad language suggesting that the conjugate may be attached to either end of either strand. The examiner also relies on Fosnaugh for teaching that the conjugate can be linked with biodegradable linkers and phosphodiester linkages. See Office Action mailed March 19, 2009, page 4. Frechet has been cited by the examiner as disclosing dendrimers that can be conjugated to nucleic acids, including dsRNA. See Office Action mailed March 19, 2009, pages 4-5. Florence allegedly discloses lipophilic dendrimers having an octanol/water coefficient of 17.5. See Office Action mailed March 19, 2009, page 5.

In the Office Action mailed November 12, 2009, the examiner responds to Applicants' arguments that the prior art (including Rana) disfavors conjugation at the 5' end of the antisense strand, in particular in instances when a free hydroxyl group is not present at the 5' end. To rebut this position, the examiner point to paragraph [0272] of Rana. Based on paragraph [0272], the examiner states, "it was recognized that the 5' end of the antisense strand of a dsRNA would need to be amenable to 5' end kinase activity but [the prior art] did not necessary require the OH group [to be] present." See Office Action, page 4. The examiner then concludes that "it was known in the prior art that the 5' end of the antisense of a dsRNA did not require a free OH for RNAi and was in fact able to reduce gene expression wherein the 5' end was linked with a phosphodiester group." See Office Action, page 4.

Applicants respectfully disagree with the conclusions reached by the examiner. In paragraph [0272], cited by the examiner, Rana is simply stating that blocking the 5' OH with amino groups at the antisense strand inhibited RNAi interference activity because (a) the 5' end kinase activity is necessary for RNA interference and (b) because the kinase is known to attack the 5' OH. Rana does not teach, as suggested by the examiner, that RNAi interference can take place in instances when the OH group is not free. As understood by those of skill in the art, 5'-OH is necessary for its being phosphorylated by kinase *in vivo*, which is necessary for RNAi interference activity.

Rana repeatedly teaches throughout the specification the importance and necessity of 5' end hydroxyl of the antisense strand of an siRNA for RNAi activity, for example, in paragraphs [0084], [0248], [0255]-[0256], and [0272]. In Example III, for instance, Rana teaches that "free 5' OH groups on the antisense strand of the siRNA duplex are required for RNA interference *in vivo*." Rana demonstrates that 5' modification of the antisense strand completely abolished the RNAi effect, as the modification lacked a hydroxyl group will not be phosphorylated by kinases *in vivo*. Rana also teaches that 5' end OH group of antisense may also be required for identification by cellular factors to access to siRNA, whereas modification also blocked this access. See paragraph [0256]. These conclusions are validated in Example VI, where 5' OH groups on the antisense strand of the siRNA duplex are phosphorylated *in vivo* for RNAi interference activity. See paragraph [0261].

As known to those of skill in the art, if the 5' OH of the antisense strand is blocked, it cannot be further phosphorylated by kinase *in vivo*. Since *in vivo* kinase is a required process for RNA interference activity, one skilled in the art would not have blocked the 5' end of antisense strand with the belief that the 5'-OH could later be phosphorylated *in vivo*. Thus, taking all teachings in Rana together, one skilled in the art, when reading Rana, would not have been motivated to modify 5'-OH of the antisense strand with the expectation that the dsRNA could enable RNAi interference.

Moreover, the examiner has not produced a single reference showing a dsRNA linked to a lipophilic conjugate via a phosphodiester group through the 5' end of the antisense strand, where (a) the dsRNA was able to reduce gene expression, and (b) the dsRNA did not contain a free hydroxyl group on the 5' end of the antisense strand. While the examiner points to select passages in Rana that could arguably be interpreted as not necessarily requiring a free hydroxyl group, the prior art cited by the examiner has still not successfully bridged the gap between not requiring a free hydroxyl group and showing success through the phosphodiester linkage. It was not until this invention that the inventors recognized that a highly lipophilic group can be conjugated on the 5' end of the antisense strand through the use of phosphodiester linkage.

As discussed in the specification, various references show that blocking the hydroxyl group located at the 5'-terminus of the antisense strand abolished the ability of a siRNA to interfere with the expression of its target gene. See pages 2-3 of the specification. One skilled in the art would not ignore the clear teachings of these references, including Rana, and attempt conjugation through the 5' end of the antisense strand without a free hydroxyl group with any expectation of success. Indeed, in view of the art as a whole, one would be deterred from proceeding in the manner chosen Applicants. Before this invention, there was no known means of introducing a highly lipophilic conjugate through the 5' end of the antisense strand in a manner that improved RNA interference activity and improved the biological activity of the dsRNA.

The examiner cites Fosnaugh as disclosing conjugation through the 5' end of the antisense strand, with the examiner correctly noting that there are only four places on the strand that one can conjugate. However, Applicants are not disputing that one skilled in art would not

have contemplated the possibility of conjugating at the 5' end of the antisense strand. Fosnaugh was simply stating that the disclosed conjugate can be attached in one of the four known places.

Fosnaugh is also cited for the proposition that the conjugate can be attached through known biodegradable linkers, including phosphodiester linkages. But again, the focus of Fosnaugh lies in the conjugate, not any special function or relationship that the conjugate has to a particular point of attachment or a particular linkage.

Applicants respectfully submit that the examiner cannot simply combine the three other references with Fosnaugh for the teaching (a) conjugation through the 5' end of the antisense strand and (b) the phosphodiester linkage and arrive at Applicants' claimed invention. Fosnaugh provides too many alternatives that one skilled in the art could easily pursue besides those identified by the examiner. When taking into account the full disclosure of Fosnaugh, it becomes clear that there are numerous possibilities taught within the reference (or generally known by one of ordinary skill in the art) for choosing different linkages, different conjugates, and different ways to attach the conjugate to the dsRNA. Just because Fosnaugh teaches that the particular conjugates disclosed in that reference may be placed on any position in the dsRNA does not mean that the reference teaches that any conjugate can be placed in any position in the strand with a reasonable expectation of success.

Variation in even one of the variables when modifying the references can lead to any number of different compounds and not to those of the claimed invention. The examiner has not presented any rationale for showing how one of ordinary skill would navigate through each possibility disclosed by Fosnaugh, incorporating the alternatives that would work while disregarding those that would not work. Fosnaugh itself certainly provide no guidance on why certain positions of the dsRNA should be used for attachment or why certain linkages should be utilized.

The rejection set forth by the examiner follows a similar obviousness analysis that was rejected by the Federal Circuit in *Ortho-McNeil Pharm., Inc. v. Mylan Laboratories, Inc.*, 520 F.3d 1358 (Fed. Cir. 2008). In *Ortho-McNeil*, the Court found that Ortho-McNeil's compound topiramate was not obvious over known design choices for finding diabetes drugs. In reaching this conclusion, the Federal Circuit stated that Mylan's expert "simply retraced the path of the inventor with hindsight, discounted the number and complexity of the alternatives, and

concluded that the invention of topiramate was obvious." *Id.* at 1364. Similarly, the examiner has not recognized the complexity and multitude of options available to Applicants at each or juncture in the process of preparing the dsRNA of the claimed invention.

One of ordinary skill in the art, the *Ortho-McNeil* Court states, would have to have some reason to select (among several unpredictable alternatives) the route that would ultimately lead to the claimed invention. 520 F.3d at 1364. The challenges of the inventive process would have prevented one of ordinary skill from traversing the multiple obstacles and arriving at the claimed invention. *Id.* at 1365. In this case, like *Ortho-McNeil*, one of ordinary skill would have to have a rationale for selecting the particular route, amid unpredictable alternatives, that leads to the claimed invention. Applicants respectfully submit that such a rationale has not been shown by the examiner.

When confronted with the problem that Applicants faced before this invention, one skilled in the art would glean no useful information from Fosnaugh to assist in solving the recognized problem. Certainty, one skilled in the art would not interpret Fosnaugh as teaching that difficulties associated with conjugating through the 5' end of the antisense strand could be overcome by its broad, generic disclosures. Just because Fosnaugh discloses that conjugating may take place at both ends of both strands and just because that phosphodiester linkages are a type of linkage that can be used to conjugate does not mean that Fosnaugh provides the motivation for combining these two features to cure a problem in the art that Fosnaugh does not even mention.

The examiner must provide an articulated reasoning for why one skilled in the art would combine the references in a manner that would lead to Applicants' claimed invention. In particular, MPEP § 2143.01 states that the fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art. The same section of the MPEP states that the mere statement that the claimed invention is within the capabilities of one of ordinary skill in the art is not sufficient by itself to establish *prima facie* obviousness. Rejections of obviousness cannot be sustained by such conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness. This is especially true in cases involving new chemical compounds, where it remains necessary to identify some reason that

would have led a chemist to modify a known compound in a particular manner to establish *prima facie* obviousness. See *Takeda Chemical Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007).

In this case, Kay is the primary reference. Aside from being deficient in the two areas discussed above in the context of Fosnaugh (no disclosure relating to conjugation through the 5' end of the antisense strand and no disclosure relating to a phosphodiester linkage), Kay additionally does not disclose a lipophilic conjugate. Nor does Fosnaugh for that matter. For the lipophilic group, the examiner relies on Frechet and Florence.

Frechet and Florence describe a lipophilic conjugate, in this case a dendrimer compound, that the examiner has substituted for the conjugate disclosed in Kay. According to the examiner, one skilled in the art would have wanted to incorporate a lipophilic group such as a dendrimer onto the dsRNA to mediate cellular uptake of the dsRNA more efficiently in methods of targeting HCV as taught by Kay. See Office Action mailed March 19, 2009, page 5.

The examiner then attempts to explain why these disclosures should be combined with Fosnaugh. This is where it gets shaky. To utilize the broad discloses of Fosnaugh, discussed above, the examiner states that "it would have been a design choice and a matter of routine experimentation." See Office Action mailed March 19, 2009, page 5. The motivation provided by the examiner ends there. The following discussion relates back to the motivation to utilize the dendrimers compounds and the benefits associated with lipophilic conjugates. See Office Action, pages 5-6.

Applicants respectfully submit that the examiner has not provided the detailed reasoning for why one skilled in the art would choose to conjugate this particular lipophilic compound (a) at the 5' end of the antisense strand, and (b) through a phosphodiester linkage. The problems associated with conjugating at the 5' end of the antisense strand--problems that have been well documented by Applicants--need to be keenly observed in making this analysis. One skilled in the art, knowing all the problems and difficulties in making this type of conjugation would be much less likely to try it. This is not the case where a reference recognizes the problem and teaches specific ways to overcome it. Fosnaugh is completely silent on this art-recognized problem; the 5' end of the antisense strand was provided as part of a comprehensive disclosure suggesting that Fosnaugh's particular conjugate could be attached through any means possible.

Fosnaugh was simply trying to cover all the bases--and one skilled in the art would read it that way.

Accordingly, Applicants respectfully request that the examiner withdraw this rejection under § 103.

III. Rejection of claims 86, 94-98, and 110-119 under 35 U.S.C. § 103

Claims 86, 94-98, and 110-119 were rejected under 35 U.S.C. § 103 as being unpatentable over the combination of Kay, Fosnaugh, Manoharan I, and Cook and evidenced by Manoharan II. As much of the basis for this rejection parallels the other § 103 rejection, discussed above, Applicants refer to those comments, particularly those comments directed towards Kay and Fosnaugh, in distinguishing the claimed invention over the cited prior art of this rejection.

There is an additional deficiency in this rejection, however, that merits attention. In the earlier § 103 rejection, the examiner states that neither Kay nor Fosnaugh taught a lipophilic group. See Office Action mailed March 19, 2009, page 4. The examiner relied on Frechet and Florence and their disclosure relating to the dendrimer compounds having a relatively high $\log K_{ow}$ value to teach this element of the claimed invention. See Office Action mailed March 19, 2009, pages 4-5.

In this rejection, the description of Kay and Fosnaugh is repeated, along with the acknowledgement that neither reference teach a lipophilic group. See Office Action mailed March 19, 2009, page 7. However, there are no secondary references that the examiner has cited teaching a lipophilic group having a $\log K_{ow}$ exceeding 1. This limitation is recited in claim 86, one of the rejected claims. Additionally, rejected claims 94-98, 110-111, and 113-119 are all dependent upon claim 86 and thus carry all of the claim limitations recited in claim 86.

While the examiner has cited Manoharan I, Cook, and Manoharan II to disclose lipophilic groups such as fatty acids, sterols, cholesterols, aromatic groups, and carbamate cholesterol groups (see Office Action mailed March 19, 2009, pages 7-9), there is no discussion of whether any of these lipophilic groups are also lipophilic groups having a $\log K_{ow}$ exceeding 1. As known in the art, certain sterols, steroids, and cholesterol derivatives are lipophilic to the degree where they have a $\log K_{ow}$ exceeding 1, while others are not. The examiner needs to show that the

lipophilic compounds disclosed in Manoharan I, Cook, and Manoharan II meet the claim limitation relating to the $logK_{ow}$ value exceeding 1, as recited in claim 86.

Without showing this, the rejection of claims 86, 94-98, 110-111, and 114-119 as being unpatentable over the combination of Kay, Fosnaugh, Manoharan I, and Cook and evidenced by Manoharan II does not teach or suggest every element of Applicants' claims.

IV. Claims 100-102

Claims 100-102 are directed to dsRNAs where the lipophilic group has a $logK_{ow}$ exceeding 1.5, exceeding 2, and exceeding 3, respectively. The examiner has rejected these claims based on the Frechet reference, showing lipophilic dendrimer groups, and Florence, allegedly showing that the dendrimer groups have a $logK_{ow}$ of 17.5.

A closer analysis of Florence, however, reveals that the examiner cited an incorrect $logK_{ow}$ value for this compound. On page 255 of Florence, the reference states "The partition coefficient of the dendrimer measured in an octanol/PBS (pH 7.4) was 17.5 and hence its log *P* value is 1.24." See top of p. 255 (carry-over paragraph from p. 254). The examiner misinterprets this passage as stating that the dendrimer has a $logK_{ow}$ of 17.5, when it is actually stating that the $logK_{ow}$ value is 1.24. The 17.5 value is simply the partition coefficient without taking into account the "log" of this value. While Florence described the partition coefficient value as a log *P* and Applicants describe the value as $logK_{ow}$, it is clear after reviewing both Applicants' specification and the complete Florence document that both terms are logs of the octanol-water partition coefficient. Compare Applicants' specification, p. 13, lines 3-21, describing the octanol-water partition coefficient with the abstract of Florence, describing the log *P* (octanol/water).

Because the dendrimer disclosed in Frechet and Florence has a octanol-water partition coefficient of less than 1.5 (1.24), these references do not suggest the additional lipophilic properties for compounds having $logK_{ow}$ of greater than 1.5, as recited in claims 100-102.

Nor do the references suggest the benefits Applicants have discovered associated with using lipophilic compounds having high $logK_{ow}$ values. Using groups having increased lipophilic properties that are covalently linked to the dsRNA has enabled the dsRNA to exhibit increased take up by cells with or without a transfection aid. The derivatized dsRNA show

surprisingly improved activity regardless of the mechanism of entry into the cell. Unlike similarly conjugated antisense RNA, the improved activity of the dsRNA of the claimed invention is independent of cellular association or receptor binding, and thus not a consequence of enhanced transport across cell membranes. See specification, page 17, lines 14-23.

Because of the highly lipophilic nature of these groups, Applicants have found that the dsRNA may be used "exclusively"; i.e. without auxiliary agents or encapsulating substances that might affect or mediate uptake of dsRNA in the cells that harbor the virus. Surprisingly, the inventors have discovered that compositions containing only naked dsRNA and physiologically acceptable solvent are taken up by cells, where the dsRNA effectively inhibits replication of the virus. The dsRNA of the claimed invention are thus particularly advantageous in that they do not require the use of an auxiliary agent to mediate uptake of the dsRNA into the cell, many of which agents are toxic or associated with deleterious side effects. See specification, page 22, line 18 to page 23, line 7.

These advantages discovered by Applicants provide an example of the unexpected results exhibited by the claimed dsRNA covalently linked to highly lipophilic groups. Additionally, these advantages demonstrate the benefits associated with the lipophilic groups, in particular with regard to lipophilic groups having a $\log K_{ow}$ exceeding 1.0, and certainly for lipophilic groups having a $\log K_{ow}$ exceeding 1.5.

Accordingly, as Frechet and Florence do not disclose lipophilic groups having a $\log K_{ow}$ exceeding 1.5 and do not disclose the benefits and surprising results discovered by Applicants associated with the lipophilic groups, Frechet and Florence do teach or suggest, in combination with the other references cited by the examiner, claims 100-102 of Applicants' claimed invention.

V. Conclusion

In view of the above remarks, Applicants respectfully request reconsideration of this application.

Except for issue fees payable under 37 C.F.R. §1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§1.16 and 1.17 which may be required,

including any required extension of time fees, or credit any overpayment to Deposit Account No. 19-2380. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. §1.136(a)(3).

Respectfully submitted,

/Jeffrey N. Townes, Reg. No. 47,142/
Jeffrey N. Townes
Reg. No. 47,142

Dated: February 12, 2010

Customer No. 84717
NIXON PEABODY LLP
Suite 900, 401 9th Street, N.W.
Washington, D.C. 20004-2128
202.585.8000